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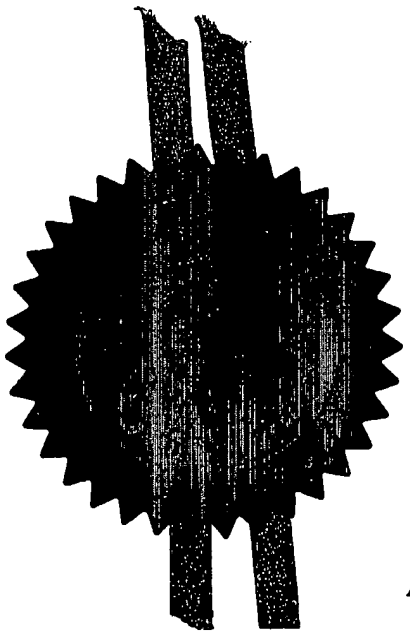

Signed Andrew Gersey

Dated 11 September 2003

Patents Form 1/77
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The Patent Office

1/77

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P01/7700 0.00-0224084.4

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The Patent Office
Cardiff Road
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1. Your reference — MG/PMS/P33126

2. Patent application number
(The Patent Office will fill in his part) — 0224084.4 — 16 OCT 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 07358700

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 07960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

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Continuation sheets of this form	0
Description	26
Claim(s)	2
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Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature J B Valentine Date 16-Oct-02

12. Name and daytime telephone number of person to contact in the United Kingdom: J B Valentine 01279 644401

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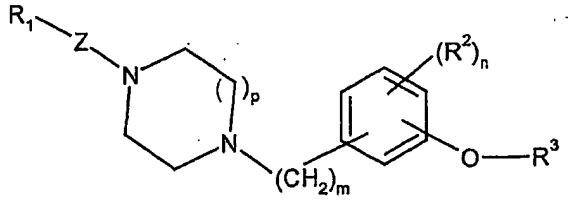
Novel Compounds

The present invention relates to novel piperazine and azepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurodegenerative disorders including Alzheimer's disease.

WO 02/76925 (Eli Lilly) describes a series of compounds which are claimed to be histamine H3 antagonists. WO 02/055496 (GlaxoSmithKline) describes a series of piperidine and piperazine derivatives which are claimed to be inducers of LDL-receptor expression.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists such as the current series could be useful for the treatment of cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I):



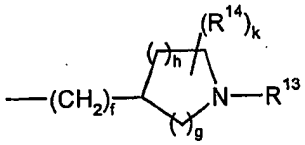
(I)

wherein:

R^1 represents -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,-heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7}

cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, $CONR^{15}R^{16}$, $NR^{15}R^{16}CO$, $NR^{15}R^{16}SO_2$ or $SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom;
Z represents a bond, CO, $CONR^{10}$ or SO_2;
p is 1 or 2;
m is 0, 1 or 2;
n is 0, 1 or 2;
R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;
R^{10} represents hydrogen or C_{1-6} alkyl, or R^{10}, together with R^1 forms a heterocyclic group;
R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent a heterocyclic group optionally substituted by one or more R^{17} groups;
R^{13} represents hydrogen, C_{1-6} alkyl, $-C_{1-6}$ alkyl-C_{1-6} alkoxy, C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or a pharmaceutically acceptable salt thereof.

Specific groups of compounds of formula (I) which may be mentioned are those as defined above wherein m represents 0.

Specific groups of compounds of formula (I) which may also be mentioned are those as defined above with the proviso that when m represents 1, R^1-Z does not represent methyl, -CO-O-$C(CH_3)_3$ or benzyl.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, diazepanyl and azepanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl and dihydroisoquinolinyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents a C_{1-6} alkyl (eg. methyl), aryl, heteroaryl (eg. benzofuran), heterocyclic (eg. benzodioxolyl) or C_{3-8} cycloalkyl group, optionally substituted by one or more halogen (eg. chlorine, fluorine or bromine), C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy) or cyano groups. More preferably, R^1 represents unsubstituted phenyl.
Preferably, Z represents a bond, CO or $CONR^{10}$. More preferably, Z represents CO.
Preferably, R^{10} represents hydrogen or C_{1-6} alkyl.
Preferably, m is 0 or 2, more preferably 0.
Preferably, n is 0.
Preferably, R^3 represents $-(CH_2)_q-NR^{11}R^{12}$.
When R^3 represents a group of formula (i), preferably f is 0, g is 2, h is 1, k is 0 and R^{13} represents hydrogen or optionally substituted C_{1-6} alkyl (eg. isopropyl or methoxyethyl)
Preferably, q is 3.
Preferably, $-NR^{11}R^{12}$ represents a heterocyclic group, more preferably piperidinyl.
Preferably, $-O-R^3$ is present at the para position of the phenyl group with respect to the rest of the compound.

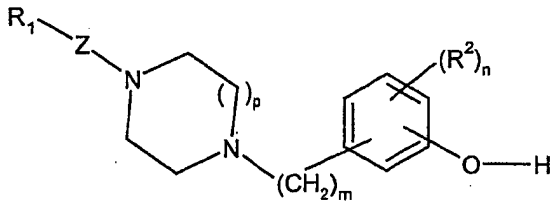
Preferred compounds according to the invention include examples E1-E52 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

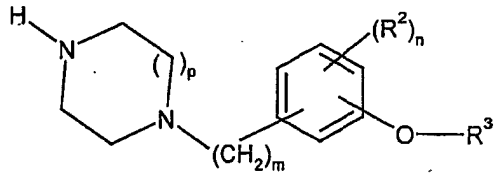
(a) reacting a compound of formula (II)



(II)

wherein R^1, Z, p, m, R^2 and n are as defined above, with a compound of formula $R^{3'}$-L^1, wherein $R^{3'}$ is as defined above for R^3 or a group convertible thereto and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or chlorine) or an optionally activated hydroxyl group; or

(b) preparing a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III)



(III)

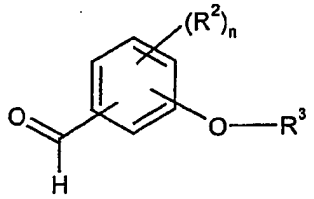
or a protected derivative thereof, wherein p, m, R^2, n and R^3 are as defined above, with a compound of formula R^1-COOX wherein, wherein R^1 is as defined above and X represents a hydrogen atom or a suitable halogen atom; or

(c) preparing a compound of formula (I) wherein Z represents SO_2 by reacting a compound of formula (III) as defined above with a compound of formula R^1-SO_2Cl, wherein R^1 is as defined above; or

(d) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ by reacting a compound of formula (III) as defined above with a compound of formula R^1-N=C=O, wherein R^1 is as defined above; or

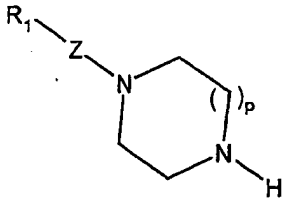
(e) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ by reacting a compound of formula (III) as defined above, sequentially with phosgene in a solvent such as toluene followed by a compound of formula $R^{10}R^1$-NH, in a solvent such as dichloromethane, wherein R^1 and R^{10} are as defined above; or

(f) preparing a compound of formula (I) wherein m represents 1 by reacting a compound of formula (IV)



(IV)

with a compound of formula (XI)



(XI)

or an optionally protected derivative thereof, wherein R^2, n, R^3, R^1, Z and p are as defined above; or

(g) deprotecting a compound of formula (I) which is protected; and

(h) interconversion to other compounds of formula (I).

When R^3 represents $-(CH_2)_q-NR^{11}R^{12}$, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide at an appropriate temperature such as reflux.

When a group $R^{3'}$ convertible to R^3 represents, for example, L^2-$(CH_2)_q$-, process (a) typically comprises an alkylation reaction using analogous conditions to those described above.

When R^3 represents a group of formula (i) and L^1 represents an optionally activated hydroxyl group, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azadicarboxylate such as diethylazaodicarboxylate at a suitable temperature such as room temperature.

Process (b) typically comprises the use of an appropriate solvent such as dichloromethane optionally in the presence of an organic or inorganic base such as potassium carbonate or in the presence of a suitable coupling agent such as 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole.

Processes (c) and (d) typically comprise the use of a suitable solvent such as 2-butanone.

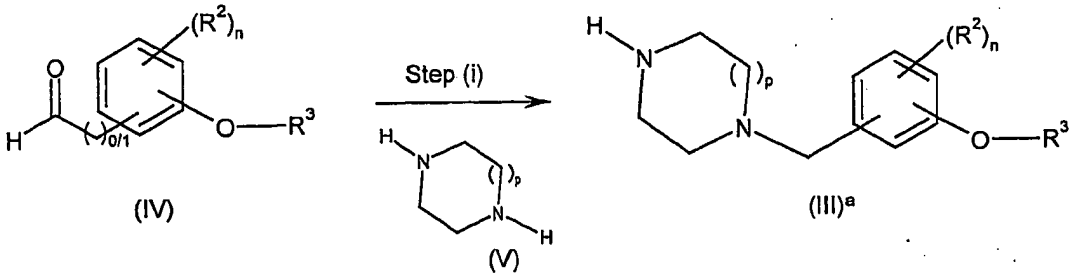
Process (e) typically comprises the use of a suitable base, such as triethylamine.

Process (f) typically comprises the use of reductive conditions (such as treatment with a borohydride eg. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, followed by optional deprotection in the event that the compound of formula (XI) is a protected derivative.

In process (g), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (h) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, compounds of formula (I) wherein R^3 represents a group of formula (i) may be interconverted at the R^{13} position by reaction with an alkyl halide such as 1-chloro-2-methoxyethane in the presence of a base such as potassium carbonate in a suitable solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide. Such interconversion may also be carried out by reductive amination, for example, with acetone in the presence of a borohydride such as sodium triacetoxyborohydride and optionally an acid such as acetic acid in a suitable solvent such as dichloromethane.

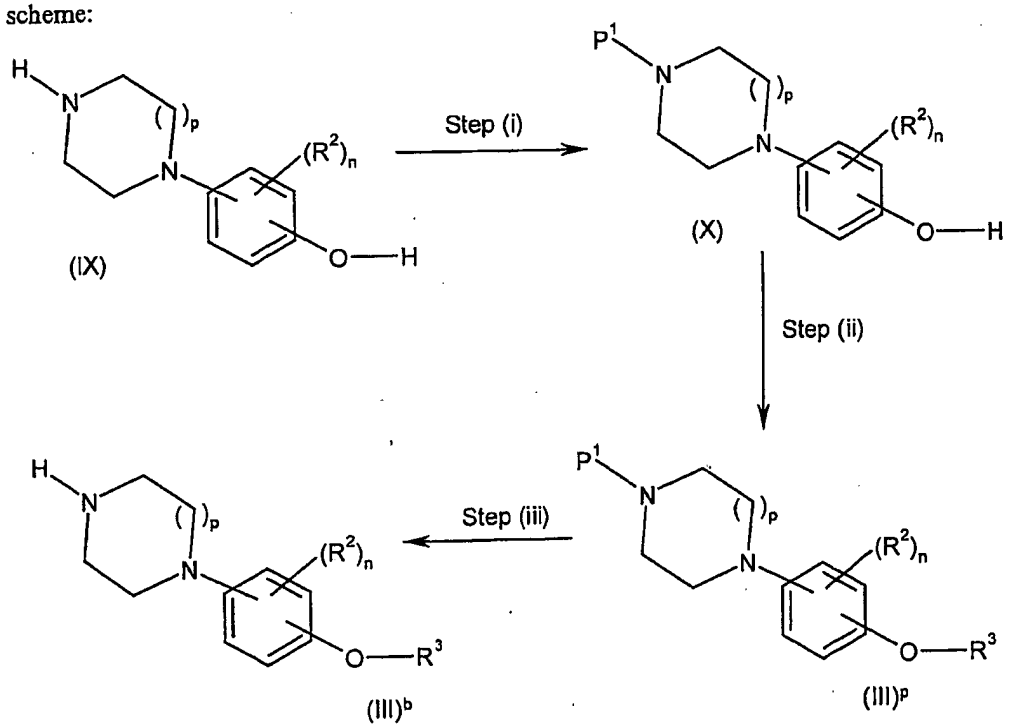
Compounds of formula (II) and (III) wherein m is 1 or 2 may be prepared in accordance with the following scheme:



wherein R^2, n, R^3, p are as defined above and the compound of formula (V) may be optionally protected.

Step (i) may be performed in an analogous manner to that described for process (f) above.

Compounds of formula (III) wherein m is 0 may be prepared in accordance with the following scheme:



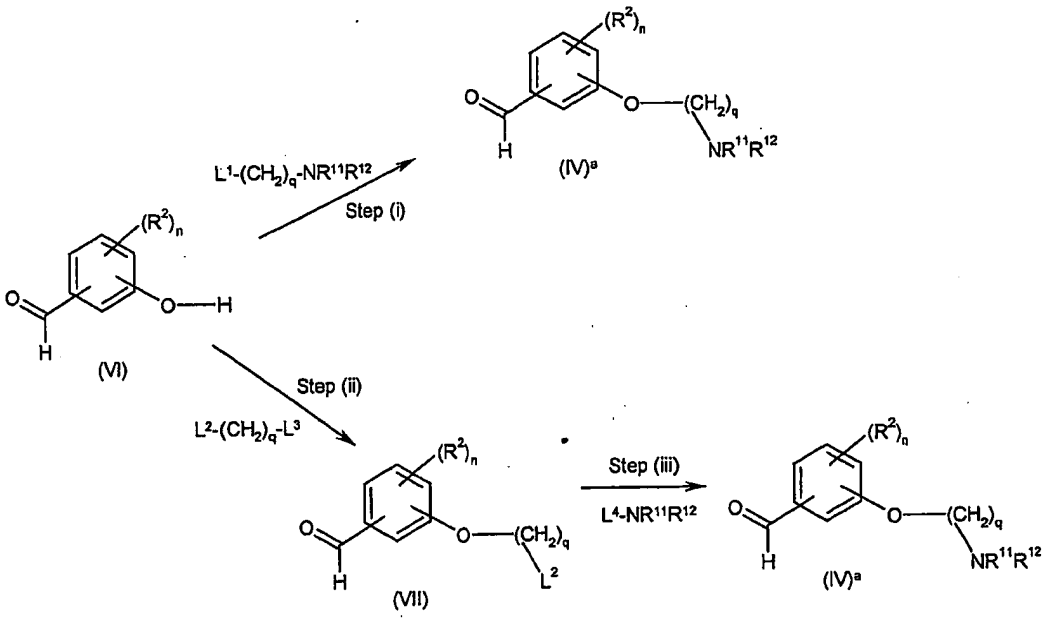
wherein p, R^2, n and R^3 are as defined above and P^1 represents a suitable protecting group (such as Boc).

Step (i) may be performed when P^1 represents Boc by reacting a compound of formula (IX) with di-t-butyl carbonate in the presence of a suitable base (eg. triethylamine) in the presence of a suitable solvent (eg. dichloromethane) at a suitable temperature (eg. room temperature).

Step (ii) may be performed in an analogous manner to the procedures shown below for the preparation of compounds of formula (IV).

Step (iii) typically comprises a deprotection reaction, for example, when P^1 represents Boc deprotection may typically comprise reaction of a compound of formula $(III)^p$ with hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

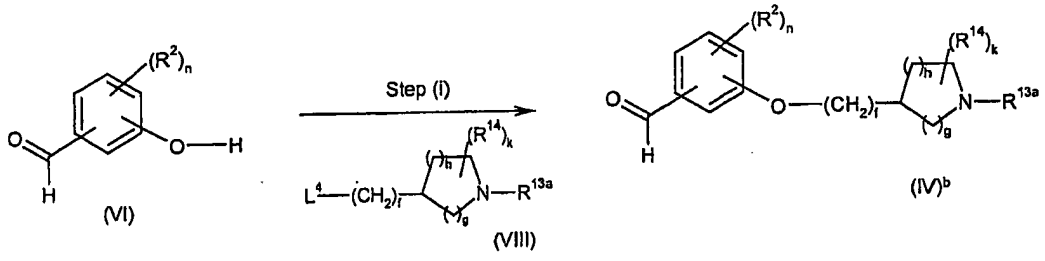
Compounds of formula (IV) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following scheme:



wherein R^2, n, q, R^{11}, R^{12} are as defined above and L^1, L^2, L^3 and L^4 represent suitable leaving groups (eg. halogen atoms, such as bromine or chlorine).

Steps (i), (ii) and (iii) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (IV) wherein R^3 represents a group of formula (i) as defined above may be prepared in accordance with the following scheme:



wherein R^2, n, f, g, h, k, are as defined above, L^4 represents a suitable leaving group such as a halogen atom or a hydroxyl group and R^{13a} is as defined above for R^{13} or a protecting group such as t-butoxycarbonyl, followed by optional deprotection.

Step (i) may be performed using similar conditions to those described for process (a) above.

Compounds of formula (II) wherein m is 0 may be prepared by a deprotection reaction of a compound of formula (IX) as defined above, followed by an analogous process to those described in processes (b), (c), (d) and (e) above, optionally followed by hydrolysis treatment to re-generate the free hydroxyl group of formula (II).

Compounds of formula (II) wherein m is 1 or 2 may be prepared from a compound of formula (IV) as defined above in an analogous process to that defined above to prepare compounds of formula $(III)^a$ followed by an analogous process to those described in processes (b), (c), (d) and (e) above, optionally followed by hydrolysis treatment to re-generate the free hydroxyl group of formula (II).

Compounds of formula (XI) may be prepared from the corresponding piperazine or diazepane by analogous procedures to those described in processes (b), (c), (d) and (e) above.

Compounds of formula (V), (VI), (VIII) and (IX) are either known or may be prepared in accordance with known procedures.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive dysfunction, epilepsy, neuropathic pain, inflammatory pain, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia, attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular neurodegenerative disorders including Alzheimer's disease.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert -butyl ester (D1)

To a solution of the product of 4-(3-(piperidin-1-yl)propoxy)benzaldehyde (WO 02/12214 A2) (1.90g, 7.68mmol) in dichloromethane (25ml) was added 1-N *tert* butoxy carbonyl piperazine (1.57g, 8.45mmol) followed by acetic acid (1ml), and the reaction stirred for 1 hour at room temperature, then treated with sodium triacetoxy borohydride (2g, 9.61mmol) and stirred for 16 hours at room temperature. The reaction was then diluted with saturated sodium bicarbonate solution and extracted with dichloromethane. The dichloromethane was then washed sequentially with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title compound (1.586g, 50%); MS (ES+), m/e 418 $[M+H]^+$.

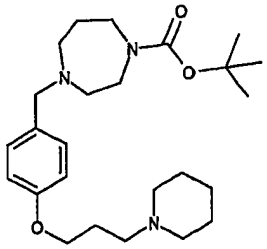
Description 2

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine trihydrochloride (D2)

To a solution of 4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid tert -butyl ester (D1) (1.576g, 3.76mmol) in a (1:1) mixture of dichloromethane and methanol (20ml) was added a 1M solution of hydrogen chloride in diethyl ether (20ml) and the reaction stirred for 5 hours at room temperature. The solvent was then evaporated *in vacuo* and the resulting residue triturated with diethyl ether to afford the title product (1.5g, 93%); MS (ES+), m/e 318 $[M+H]^+$.

Description 3

4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3)

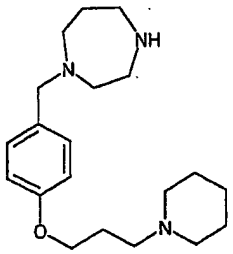


The title compound (D3) was prepared from [1,4]diazepane-1-carboxylic acid *tert*-butyl ester using the method of Description 1 (D1).

MS(ES+) m/e 432 $[M+H]^+$.

Description 4

1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4)



4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D3) (2.27g, 5.27mmole) was dissolved in dichloromethane (10ml), treated with trifluoroacetic acid (5ml) and stirred at room temperature under argon for 2 hours. The solvent was removed in vacuo and the residue dissolved in methanol and passed down an SCX column (10g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated in vacuo to afford the title compound (1.57g).
MS(ES+) m/e 332 $[M+H]^+$.

Description 5

4-(4-Formyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D5)

4-Hydroxybenzaldehyde (2.0g, 16.4mmole) was dissolved in tetrahydrofuran (20ml) and treated with 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (4.1g, 20.5mmole) and triphenylphosphine (5.4g, 20.5mmole). The mixture was cooled in an ice bath, treated with diethyl azodicarboxylate (3.2ml, 20.5mmole) and allowed to stir at room temperature for 36 hours. The reaction mixture was diluted with ethyl acetate, washed with sodium hydroxide solution (2M), sodium bicarbonate solution and brine. The organic layer was dried under magnesium sulphate, filtered and the solvent removed in vacuo. The title compound (1.85g) was obtained by column chromatography eluting with ethyl acetate/hexane (1:4).
^{1}H NMR (CDCl3) δ 9.88 (1H, s), 7.85-7.82 (2H, d), 7.02-6.99 (2H, d), 4.65-4.59 (1H, m), 3.74-3.65 (2H, m), 3.43-3.33 (2H, m), 2.04-1.92 (2H, m), 1.82-1.77 (2H, m), 1.47 (9H, s).

Description 6

4-(4-Piperazin-1-ylmethyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D6)

The title compound (D6) was prepared from 4-(4-formyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D5) and piperazine using the method described in Description 3 (D3). MS(ES+) m/e 376 $[M+H]^+$.

Description 7

4-{4-[4-(1-Phenyl-methanoyl)-piperazin-1-ylmethyl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester (D7)

The title compound (D7) was prepared from 4-(4-piperazin-1-ylmethyl-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D6) and benzoyl chloride using the method described in Example 24 (E24). MS(ES+) m/e 480 $[M+H]^+$.

Description 8

4-(4-Hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D8)

Di-*tert*-butyl dicarbonate (10.1 g; 1.1 eq) was added portion wise to 4-piperazin-1-yl-phenol (Chem. Pharm. Bull. 49(10), 1314 (2001)) (7.5 g; 42.1 mM) and triethylamine (6.4 ml; 1.1 eq) in dichloromethane (150 ml). The resulting mixture was stirred at room temperature for 18 hours The reaction was washed with water (2x100 ml), dried (sodium sulphate) and the solvent removed by evaporation *in vacuo*. The residue was purified by column chromatography on silica eluting with 4-1 hexane-ethyl acetate to afford the title compound as an off-white solid (4.71 g)
MS (ES+) m/e 279 $[M+H]^+$.

Description 9

4-[4-(3-Chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D9)

A mixture of 4-(4-hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D8) (4.0 g; 14.4 mM), 1-bromo-3-chloro propane (1.70 ml; 1.2 eq) and potassium carbonate (4.0 g; 2 eq) in butan-2-one (100 ml) was heated at reflux for 18 hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was purified by column chromatography on silica eluting with 4-1 hexane – ethyl acetate to afford the title compound as a colourless viscous oil (3.8 g)
MS (ES+) m/e 355 $[M+H]^+$.

Description 10

4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10)

A mixture of 4-[4-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D9) (4.0 g; 11.3 mM), piperidine (2.23 ml; 2 eq), potassium carbonate (3.73 g; 2.4 eq) and potassium iodide (3.74 g; 2 eq) in butan-2-one (100 ml) was heated at reflux for 3 days. The mixture was allowed to cool to room temperature, filtered and evaporated to give the title compound as a pale yellow solid (4.6 g)
MS (ES+) m/e 404 $[M+H]^+$.

Description 11

1-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D11)

A solution of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D10) (1.0 g; 2.48 mM) in trifluoroacetic acid (5 ml) was stirred at room temperature for 60 minutes. The resulting mixture was purified on an SCX ion exchange cartridge to afford the title compound as a colourless crystalline solid (0.76 g)
MS (ES+) m/e 304 $[M+H]^+$.

Description 12

4-(3-Hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12)

Prepared from 3-piperazin-1-yl-phenol (Chem. Pharm. Bull. 49(10), 1314 (2001)) using the same method described in Description 8 (D8).
MS (ES+) m/e 279 $[M+H]^+$.

Description 13

4-[3-(3-Chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13)

Prepared from 4-(3-hydroxy-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (D12) using the same method described in Description 9 (D9).
MS (ES+) m/e 355 $[M+H]^+$.

Description 14

4-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14)

Prepared from 4-[3-(3-chloro-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D13) using the same method described in Description 10 (D10).
MS (ES+) m/e 404 $[M+H]^+$.

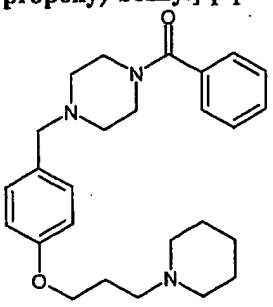
Description 15

1-[3-(3-Piperidin-1-yl-propoxy)-phenyl]-piperazine (D15)

Prepared from 4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine-1-carboxylic acid *tert*-butyl ester (D14) using the same method described in Description 11 (D11).
MS (ES+) m/e 304 $[M+H]^+$.

Example 1

1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E1)



N-Cyclohexylcarbodiimide, N-methyl polystyrene HL (200-400 mesh) 1.8mMol/g (650mg, 1.172mmol) was suspended in a (1:1) mixture of dichloromethane and dimethylformamide and treated sequentially with benzoic acid (72mg, 0.58mmol), 1-hydroxybenzotriazole hydrate (80mg, 0.58mmol) and stirred for 10 minutes at room temperature. A solution of 1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazine trihydrochloride (D2) (125mg, 0.29mmol) in dichloromethane (1ml) and triethylamine (0.13ml, 0.87mmol) was then added to the reaction and stirred at room temperature for 16 hours. After filtration, the filtrate was applied to a Mega Bond elute SCX ion exchange column washing sequentially with water and methanol, followed by 0.880 ammonia/methanol (1:10) to elute the crude reaction mixture. Purification by silica gel

chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (0.5:4.5:95) to afford the title product (95mg, 77%); MS (ES+), m/e 422 $[M+H]^+$.

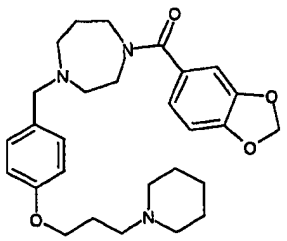
Examples 2-11

Examples 2-11 (E2-E11) were prepared from Description 2 (D2) using an analogous method to that described in Example 1 (E1) by substituting benzoic acid for the appropriate acid indicated in the table.

Example	Acid	Mass Spectrum
1-Benzo[1,3]dioxol-5-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E2)	piperonylic acid	MS (ES+) m/e 466 $[M+H]^+$
1-Naphthalen-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E3)	2-naphthoic acid	MS (ES+) m/e 472 $[M+H]^+$
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E4)	3,5-dichlorobenzoic acid	MS (ES+) m/e 491/493 $[M+H]^+$
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E5)	3-methyl, 4-bromo benzoic acid	MS (ES+) m/e 515/517 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E6)	2-methoxy benzoic acid	MS (ES+) m/e 452 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E7)	3,4-dichloro benzoic acid	MS (ES+) m/e 491/493/495 $[M+H]^+$
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanoyl)-benzonitrile (E8)	4-cyano benzoic acid	MS (ES+) m/e 447 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E9)	4-fluoro benzoic acid	MS (ES+) m/e 440 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E10)	4-bromo benzoic acid	MS (ES+) m/e 500/502 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-piperazin-1-yl}-methanone (E11)	2-benzofuran carboxylic acid	MS (ES+) m/e 462 $[M+H]^+$

Example 12

1-Benzo[1,3]dioxol-5-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E12)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmole) was dissolved in dichloromethane (5ml) and treated sequentially with benzo[1,3]dioxole-5-carboxylic acid (125mg, 0.75mmole), 1,3-dicyclohexylcarbodiimide (155mg, 0.75mmole) and 1-hydroxybenzotriazole hydrate (101mg, 0.75mmole). The mixture was allowed to stir at room temperature under argon for 12 hours, diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated in vacuo to afford the title compound (127mg). MS(ES+) *m/e* 480 $[M+H]^+$.

Examples 13-15

Examples 13-15 (E13-E15) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table.

Example	Carboxylic acid	Mass Spectrum
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E13)	Benzoic acid	MS(ES+) m/e 436 $[M+H]^+$
1-Naphthalen-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E14)	Naphthalene-2-carboxylic acid	MS(ES+) m/e 486 $[M+H]^+$
1-(3,5-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E15)	3,5-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$

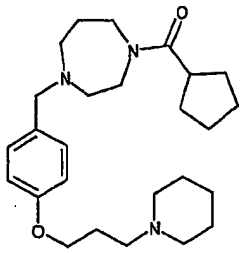
Examples 16-23

Examples 16-23 (E16-E23) were prepared from Description 4 (D4) using an analogous method to that described in Example 12 (E12) by substituting benzo[1,3]dioxole-5-carboxylic acid for the appropriate acid indicated in the table followed by further purification by column chromatography on silica gel eluting with ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Carboxylic acid	Mass Spectrum
1-(4-Bromo-3-methyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E16)	4-Bromo-3-methyl-benzoic acid	MS(ES+) m/e 529 $[M+H]^+$
1-(2-Methoxy-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E17)	2-Methoxy-benzoic acid	MS(ES+) m/e 466 $[M+H]^+$
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanoyl)-benzonitrile (E18)	4-Cyano-benzoic acid	MS(ES+) m/e 461 $[M+H]^+$
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E19)	4-Fluoro-benzoic acid	MS(ES+) m/e 454 $[M+H]^+$
1-(4-Bromo-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E20)	4-Bromo-benzoic acid	MS(ES+) m/e 515 $[M+H]^+$
1-Benzofuran-2-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E21)	Benzofuran-2-carboxylic acid	MS(ES+) m/e 476 $[M+H]^+$
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E22)	3,4-Dichloro-benzoic acid	MS(ES+) m/e 505 $[M+H]^+$
1-Cyclopropyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E23)	Cyclopropane carboxylic acid	MS(ES+) m/e 400 $[M+H]^+$

Example 24

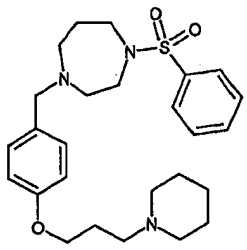
1-Cyclopentyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepan-1-yl}-methanone (E24)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmole) was dissolved in dichloromethane (5ml), treated with cyclopentyl acid chloride (80mg, 0.60mmole), potassium carbonate (83mg, 0.60mmole) and allowed to stir at room temperature under argon for 12 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated in vacuo to afford the title compound (56mg). MS(ES+) *m/e* 428 $[M+H]^+$.

Example 25

1-Benzenesulfonyl-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E25)



1-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (D4) (100mg, 0.30mmole) was dissolved in 2-butanone (5ml), treated with benzenesulfonyl chloride (57mg, 0.32mmole) and allowed to stir at room temperature under argon for 2 hours. The reaction mixture was diluted with methanol and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated in vacuo to afford the title compound (91mg). MS(ES+) *m/e* 472 $[M+H]^+$.

Examples 26-28

Examples 26-28 (E26-E28) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table.

Example	Sulfonyl Chloride	Mass Spectrum
1-(Naphthalene-2-sulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E26)	Naphthalene-2-sulfonyl chloride	MS(ES+) m/e 522 $[M+H]^+$
1-(4-Fluoro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-	4-Fluoro-benzenesulfonyl	MS(ES+) m/e 490 $[M+H]^+$

[1,4]diazepane (E27)	chloride	
1-(4-Bromo-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E28)	4-Bromo-benzenesulfonyl chloride	MS(ES+) m/e 552 $[M+H]^+$

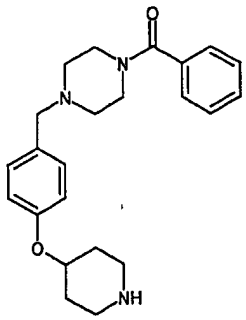
Examples 29-31

Examples 29-31 (E29-E31) were prepared from Description 4 (D4) using an analogous method to that described in Example 25 (E25) by substituting benzenesulfonyl chloride for the appropriate sulfonyl chloride indicated in the table followed by further purification by column chromatography on silica gel eluting with ammonia/methanol/dichloromethane (0.5:4.5:95).

Example	Sulfonyl Chloride	Mass Spectrum
1-(3,5-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E29)	3,5-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
1-(3,4-Dichloro-benzenesulfonyl)-4-[4-(3-piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane (E30)	3,4-Dichloro-benzenesulfonyl chloride	MS(ES+) m/e 540 $[M+H]^+$
4-{4-[4-(3-Piperidin-1-yl-propoxy)-benzyl]-[1,4]diazepane-1-sulfonyl}-benzonitrile (E31)	4-Cyano-benzenesulfonyl chloride	MS(ES+) m/e 497 $[M+H]^+$

Example 32

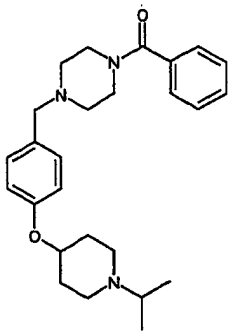
1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32)



The title compound (E32) was prepared from 4-{4-[4-(1-phenyl-methanoyl)-piperazin-1-ylmethyl]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester (D7) using the method described in Description 4 (D4). MS(ES+) m/e 380 $[M+H]^+$.

Example 33

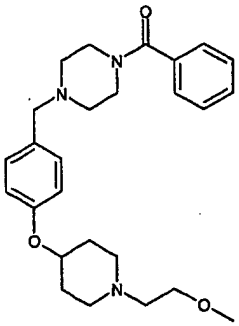
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-1-phenyl-methanone (E33)



The title compound (E33) was prepared from 1-phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) and acetone using the method described in Description 1 (D1). MS(ES+) m/e 422 $[M+H]^+$.

Example 34

1-(4-{4-[1-(2-Methoxy-ethyl)-piperidin-4-yloxy]-benzyl}-piperazin-1-yl)-1-phenyl-methanone (E34)



1-Phenyl-1-{4-[4-(piperidin-4-yloxy)-benzyl]-piperazin-1-yl}-methanone (E32) (150mg, 0.40mmole) was dissolved in 2-butanone and treated with 1-chloro-2-methoxy-ethane (0.08ml, 0.80mmole), potassium carbonate (132mg, 0.96mmole) and potassium iodide (159mg, 0.96mmole). The reaction mixture was heated under reflux for 24 hours. The mixture was allowed to cool to room temperature, acidified by the addition of glacial acetic acid and passed down an SCX column (2g) eluting with methanol followed by ammonia/methanol (1:9). The basic fractions were combined and concentrated in vacuo to afford the title compound (76mg). MS(ES+) *m/e* 438 $[M+H]^+$.

Examples 35-37

Examples 35-37 (E35-E37) were prepared in accordance with the following general synthesis:

The appropriate acid chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Acid Chloride	Mass Spectrum

1-Cyclopropyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E35)	Cyclopropane carbonyl chloride	MS (ES+) m/e 372 $[M+H]^+$.
1-Phenyl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E36)	Benzoyl chloride	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E37)	3,4-Dichlorobenzoyl chloride	MS (ES+) m/e 477 $[M+H]^+$.

Examples 38-39

Examples 38-39 (E38-E39) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 36 and 37, respectively.

Example	Mass Spectrum
1-Phenyl-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E38)	MS (ES+) m/e 408 $[M+H]^+$.
1-(3,4-Dichloro-phenyl)-1-{4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazin-1-yl}-methanone (E39)	MS (ES+) m/e 477 $[M+H]^+$.

Examples 40-42

Examples 40-42 (E40-E42) were prepared in accordance with the following general synthesis:

The appropriate sulphonyl chloride (1.1 eq) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) and potassium carbonate (55 mg; 1.5 eq) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Sulfonyl Chloride	Mass Spectrum
1-Methanesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E40)	Methane sulfonyl chloride	MS (ES+) m/e 382 $[M+H]^+$.
1-Benzenesulphonyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E41)	Benzene sulfonyl chloride	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E42)	3,4-Dichlorobenzene sulfonyl chloride	MS (ES+) m/e 513 $[M+H]^+$.

Examples 43-45

Examples 43-45 (E43-E45) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 40, 41 and 42, respectively.

Example	Mass Spectrum
1-Methanesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E43)	MS (ES+) m/e 382 $[M+H]^+$.

1-Benzenesulphonyl-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E44)	MS (ES+) m/e 444 $[M+H]^+$.
1-(3,4-Dichloro benzenesulphonyl)-4-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (E45)	MS (ES+) m/e 513 $[M+H]^+$.

Examples 46-47

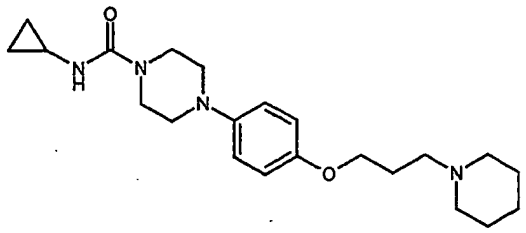
Examples 46-47 (E46-E47) were prepared in accordance with the following general synthesis:

The appropriate isocyanate (1.1 eq) was added to 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (100 mg; 0.33 mM) in butan-2-one (2 ml). The resulting mixtures were stirred at room temperature for 3 hours and then purified on SCX ion exchange cartridges to afford the title compounds.

Example	Isocyanate	Mass Spectrum
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E46)	Isocyanatobenzene	MS (ES+) m/e 423 $[M+H]^+$.
4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E47)	3,4-Dichloroisocyanato benzene	MS (ES+) m/e 492 $[M+H]^+$.

Example 48

4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid cyclopropylamide (E48)



To a solution of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mM) in dry dichloromethane (3 ml) was added drop wise a 20% solution of phosgene in toluene (0.5 ml; ~2 eq) and the resulting mixture stirred for 1 hour. The solvent was removed by evaporation and the resulting white powder dissolved in dry dichloromethane (4 ml). Triethylamine (0.14 ml: 2 eq) was added followed by cyclopropylamine (0.1 ml; 3 eq) and the mixture stirred for 18 hours. The solvent was removed by evaporation *in vacuo* and the residue purified on a silica column eluting with 3% methanol in dichloromethane to afford the title compound as a white solid (155 mg)

MS (ES+) m/e 387 $[M+H]^+$.

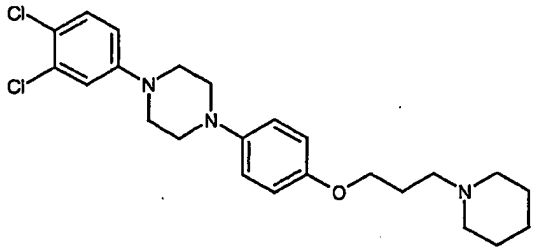
Examples 49-50

Examples 49-50 (E49-E50) were prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same procedure as described in Examples 46 and 47, respectively.

Example	Mass Spectrum
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid phenylamide (E49)	MS (ES+) m/e 423 $[M+H]^+$.
4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide (E50)	MS (ES+) m/e 492 $[M+H]^+$.

Example 51

1-(3,4-Dichloro-phenyl)-4-[4-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E51)

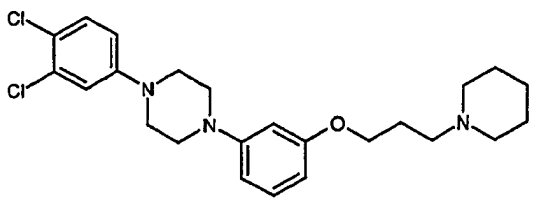


Tris(dibenzylidineacetone) di palladium (0) (5 mol%; 23 mg) was added to a mixture of 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D11) (150 mg; 0.49 mM), 3,4-dichloro bromo benzene (160 mg; 1.2 eq), sodium *tert*-butoxide (71 mg; 1.1 eq) and racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7.5 mol%; 24 mg) in dry toluene (3ml). The resulting mixture was heated at reflux under argon for 18 hours. The reaction was allowed to cool to room temperature and diluted with ethyl acetate (10 ml). The resulting solids were removed by filtration and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica eluting with 3% methanol in dichloromethane to afford the title compound as a buff solid (45 mg)

MS (ES+) m/e 448 $[M+H]^+$.

Example 52

1-(3,4-Dichloro-phenyl)-4-[3-(3-Piperidin-1-yl-propoxy)-phenyl] piperazine (E52)



The title compound (E52) was prepared from 1-[3-(3-piperidin-1-yl-propoxy)-phenyl]-piperazine (D15) using the same method as described in Example 51 (E51).
MS (ES+) m/e 448 $[M+H]^+$.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

The histamine H3 cDNA was isolated from its holding vector, pCDNA3.1 TOPO (InVitrogen), by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α *E. coli* host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the *sh ble* gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).
CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.
10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm

Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10μl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/μl or 50μCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80μl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80μl which contains 7.5μg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.

The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-

Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

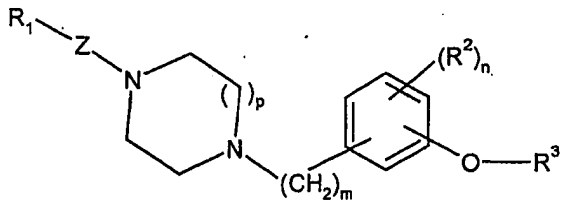
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-52 were tested in the histamine H3 functional antagonist assay and exhibited antagonism in the following range: 6.5-10.5 pK_b. More particularly, the compounds of Examples E1, E31, E33, E35-37, E40-42, E46-48 and E51 exhibited antagonism in the following range: 8.4-10.5 pK_b.

CLAIMS:

1. A compound of formula (I):



(I)

wherein:

R^1 represents -C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl,-heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -heterocyclyl-heterocyclyl,

wherein R^1 may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamido, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, $CONR^{15}R^{16}$, $NR^{15}R^{16}CO$, $NR^{15}R^{16}SO_2$ or $SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together may be fused to form a 5- to 7- membered non-aromatic heterocyclic ring optionally interrupted by an O or S atom;

Z represents a bond, CO, $CONR^{10}$ or SO_2;

p is 1 or 2;

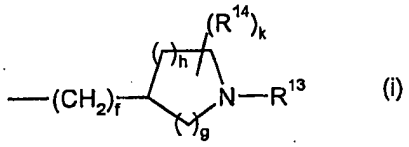
m is 0, 1 or 2;

n is 0, 1 or 2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

R^{10} represents hydrogen or C_{1-6} alkyl, or R^{10}, together with R^1 forms a heterocyclic group;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent a heterocyclic group optionally substituted by one or more R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, -C_{1-6} alkyl-C_{1-6} alkoxy, C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH, diC_{1-6} alkylamino, C_{1-6} alkoxy or heterocyclyl;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E52 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.